

AN ATTEMPT AT A NATURAL CLASSIFICATION OF THE STEROIDS

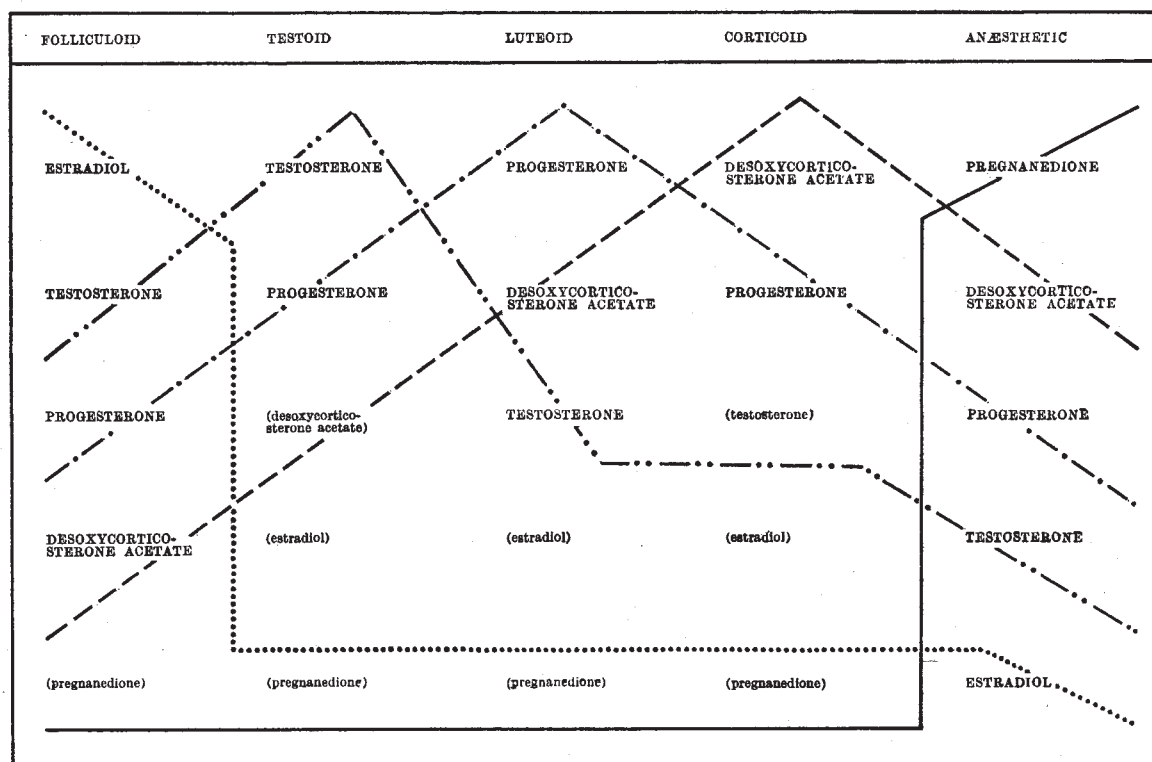
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THE manifold and overlapping activities of hormonal steroids tend to give the impression that there is no orderly pharmacological correlation among them. It is known that testoid or 'male' compounds may have folliculoid or 'female' hormone-like activities, that adrenal steroids may imitate the hormone of the corpus luteum, and so forth. An addi-

vesicles and prostate, are subordinate to the testoid action, and so forth. There is no such parallelism in the degree to which a compound exhibits any two of the so-called independent actions. However, even among these, only the folliculoid and anaesthetic potencies are ever demonstrable in a steroid in the complete absence of all other hormonal effects. Furthermore, with the exception of the purely anaesthetic compounds, all hormonal steroids exert some degree of folliculoid activity, and conversely, all hormones are active as anaesthetics.

It has now been observed that the above rules, as well as other regularities among the steroids, can readily be visualized by their classification into the systematic table shown below. The most active representatives of five independent actions have been

SYSTEMATIC TABLE OF THE STEROIDS.



tional complication has recently been introduced by the observation that under suitable experimental conditions all steroid hormones exhibit anaesthetic properties.

However, certain regularities are detectable. Thus it has been shown that some steroid hormone actions are independent of each other, while others are strictly interdependent. The folliculoid, testoid, luteoid, corticoid, anaesthetic, renotropic and spermatogenic activities all have proved to be independent of each other inasmuch as there is no parallelism in the ability of compounds to exhibit these various effects. On the other hand, such responses as vaginal cornification, uterine enlargement, testis atrophy and the cure of castration changes in the hypophysis are all subordinate to the folliculoid action. Hence the degree to which a compound is able to exhibit any one of these effects is proportionate to its other folliculoid activities. Similarly the comb-growth effect, as well as the stimulation of the seminal

selected and arranged from left to right according to decreasing order of folliculoid potency. (Since the most potent representatives of the renotropic and spermatogenic series have not been definitely identified as yet, these actions are not considered here. However, according to the folliculoid effect of the known prominent representatives of these groups, they should both be inserted next to testosterone.) It will be noted that the folliculoid activity of all these compounds, except estradiol, is 'masked' and detectable only under certain experimental conditions. Furthermore, for the purpose of this discussion prostatic enlargement is considered sufficient for the demonstration of testoid activity. The potency ratings for folliculoid^{1,2}, testoid³, luteoid⁴, corticoid^{5,6,7,8} and anaesthetic⁹ activities have all been taken from publications based on assays performed before this system was devised. Desoxycorticosterone acetate has been chosen as the most active representative of the corticoid series as it is the only highly active

member of this group which has been adequately studied for all five independent actions. In each column representing a certain type of activity the inert compounds are inserted in brackets below the active compounds of the group. When the steroids are so arranged according to decreasing folliculoid activity in the first line of the table, the most active representatives of the folliculoid, testoid, luteoid, corticoid and anaesthetic compounds appear in the order stated. The second most active representatives of each of these five activities were placed in the second line, third place being given to the next most active compounds, and so forth.

Perusal of the table indicates that, if the steroids are arranged in the first column according to decreasing order of folliculoid activity, they are automatically in increasing order of anaesthetic potency. The position of each steroid was traced by a line through the five columns. This revealed that estradiol and pregnanedione are at the bottom of the graph, except in the column in which they are placed on top as the most active folliculoid and anaesthetic compound respectively. The three remaining compounds slowly lose height in both directions with approximately the same slope. Thus the curve described by the position of any steroid in the table exhibits a single maximum.

Prof. D. L. Thomson kindly analysed these data in order to determine whether the apparent 'orderliness' is statistically significant. Disregarding all possible *a priori* arguments from chemical relationships he found that the regularities observed in the whole scheme—allowing for the selection of the top entry in each column and giving no 'credit' for possible orderliness in the compounds found inactive in each type of test—would occur by chance only in 1 out of 2,304 trials. Hence it may be said that this particular arrangement is not due to chance, but is apparently dependent upon certain inherent natural relationships between the steroids.

The table also expresses the empirical fact that only folliculoid or anaesthetic potencies may be exhibited to the exclusion of all other independent actions, since these two are on the outer limits of the system and hence do not have to overlap with other effects. Compounds not included in this table also obey the same rules although, of course, depending upon the degree of their potency they range above or below the curves given here. Thus ethinyl-estradiol, which is somewhat more folliculoid than estradiol, describes a line parallel with that of estradiol although somewhat higher than the latter, while pregnenolone, a compound having an activity which is qualitatively similar but quantitatively inferior to that of progesterone, parallels the curve of the latter at a somewhat lower level. Acetoxy-pregnenolone, a comparatively inactive corticoid⁶, parallels the desoxycorticosterone acetate curve in a similar manner, and so forth. Among all steroids studied no exception could be found to the rule that all compounds describe curves with a single maximum when inserted in this system. The main weakness of the classification so far detected is that the activity curve of a certain compound may skip one or more points on the curve, perhaps because this particular action is so 'masked' that it is not detectable with our bio-assay methods.

The biological significance of these correlations among the steroids is not easy to interpret. It may be that the molecular structure necessary for any one activity necessarily carries within itself other pharmacological properties and that the intensity of

these decreases in direct proportion to their distance from the primary activity in the table. It is also possible that the compound placed at the peak of any one curve is partly transformed in the body into compounds with neighbouring actions which in turn yield smaller amounts of steroids in the columns next to them. Thus the degree of activity would gradually diminish in proportion to the distance in the table from the position of the original compound injected. In this sense the pure folliculoids and anaesthetics might be considered as metabolic end-products incapable of re-transformation into compounds occupying more central positions in the table. This is graphically expressed by their marginal position and the steep curve which separates them from neighbouring activities. In connexion with the observation that a compound may skip a point on the curve, we must consider the possibility that certain steroids may go through a pharmacologically inactive stage during their metabolism.

Considering the limited data available at this time, it would scarcely be justified to base any far-reaching speculations on the regularities observed. The only purpose of this communication is to direct attention to the fact that if the steroids are arranged according to the degree of their folliculoid activity, they fall into a system which permits—within limits—a prediction of their other activities.

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³ Selye, Hans, and Albert, S., *J. Pharm. and Exp. Therap.*, **76**, 137 (1942).

⁴ Selye, Hans, and Masson, Georges, *J. Pharm. and Exp. Therap.* (in the press).

⁵ Segaloff, Albert, and Nelson, Warren O., *Endocrinol.*, **31**, 592 (1942).

⁶ Selye, Hans, *Science*, **94**, 94 (1941).

⁷ Steiger, M., and Reichstein, T., *Helvet. chim. Acta*, **20**, 1164 (1937).

⁸ Schwabe, E. L., and Emery, F. E., *Proc. Soc. Exp. Biol. and Med.*, **40**, 383 (1939).

⁹ Selye, Hans, *Endocrinol.*, **30**, 437 (1942).

ORIGIN OF COSMIC RAYS

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THE hypothesis here adopted as to the mode of origin of the cosmic rays makes possible the prediction of five definite vertically incoming cosmic-ray bands. As the observer moves north from the magnetic equator, each of these five bands should begin to reach the earth at a particular latitude and continue reaching it at all more northerly latitudes. Between each latitude of first entrance of a band of particular energy and the latitude of first entrance of the band of next lower energy, there should be found a plateau of constant vertically incoming cosmic-ray energy. Four such plateaux should be experimentally observable.

The hypothesis rendering possible these predictions rests upon five major discoveries¹:

(1) The proof by Millikan and Neher that more than 60 per cent of all incoming cosmic-ray energy is of the nature of incoming charged-particle bullets, each of energy between 2 billion electron volts and 15 billion electron volts.

(2) Néddermeyer and Anderson's discovery of the production by nuclear impacts within the atmosphere